REMARKS

Applicants have carefully studied the Final Office Action mailed October 26, 2009, which issued in connection with the above-identified patent application. The present response is intended to be fully responsive to all points raised by the Examiner and is believed to place the claims in condition for allowance. Favorable consideration and allowance of the present claims are respectfully requested.

I. Pending Claims

Claims 1, 3, 4, 9-13, 15-20, 22, 23, 28-31, 33-37, 40, 45, 46, and 51-55 were pending in this application. Claims 11-13, 15-19, 29-31, 33-37, and 40 have been withdrawn from consideration as directed to non-elected invention.

By the present amendment to the claims, Claims 1 and 20 have been amended to recite that the prion protein contained in the composition is "non-infectious, non-pathogenic". Support for this amendment can be found, for example, in paragraphs [0008], [0028], [0040], [0041] and Examples 1-4 of the application as published (US Patent Publication No. 2007/0059807). Claims 1 and 20 have been also amended to recite that the prion protein in the composition is selected from the group consisting of mouse, bovine, deer, elk, and sheep prion protein. Support for this amendment can be found, for example, in paragraphs [0015], [0017], and [0037] of the application as published. Claims 1 and 20 have been further amended to recite that "the composition is suitable for mucosal administration." Support for this amendment can be found, for example, in paragraphs [0014], [0019], [0049-0050], [0066], [0068-0070], [0077-0079], and Examples 1-4 of the application as published. In addition, Claims 1 and 20 have been amended to recite that the composition "when introduced to a mammal's mucosal immune system, elicits a primarily Th-2-type immune response against an endogenous prion protein of said mammal that is associated with a mucosal IgA humoral immune response and any concomitant immunoglobulin counterpart in other bodily fluids, and is not associated with a primarily Th-1-type cytotoxic T-lymphocyte response." Support for this amendment can be found, for example, in paragraphs [0014], [0040], [0052], [0069], [0071], and [0084] of the application as published.

Claim 9 has been amended to delete the recitation of cholera toxin subunit B (CT-B) and heat-labile enterotoxin (LT). New dependent Claim 56 has been added to recite the composition of Claim 1, further comprising cholera toxin subunit B (CT-B) or heat-labile enterotoxin (LT). Support for this new claim can be found, for example, in the original Claim 9 and paragraphs [0050-0055] of the application as published.

Claim 10 has been amended to correct dependency.

Claims 54 and 55 have been canceled without prejudice or disclaimer. Applicants preserve the right to pursue the subject matter of these claims in a continuing application.

No new matter has been added as a result of these amendments.

II. Anticipation Rejection

Claims 1 and 54 have been rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent Application Publication No.: 2003/0219459 by Bachmann et al. (hereafter, "Bachmann").

As Claim 54 has been canceled, the rejection of this claim is rendered moot.

With respect to Claim 1, Applicants respectfully traverse the rejection.

Applicants note that the Examiner has reinstated the previously overcome anticipation rejection over Bachmann in light of Applicants' amendment to Claim 1 to delete the limitation "the composition is suitable for mucosal administration." In the present amendment, this limitation has been added back to claim 1.

In addition, Claim 1 has been amended to recite that the composition "when introduced to a mammal's mucosal immune system, elicits a primarily Th-2-type immune response against an endogenous prion protein of said mammal that is associated with a mucosal IgA humoral immune response and any concomitant immunoglobulin counterpart in other bodily fluids, and is not

associated with a primarily Th-1-type cytotoxic T-lymphocyte response." This functional property of the immunogenic compositions of the present invention is very important, because mucosal Th-1-type cytotoxic T-lymphocyte (CTL) responses can be very harmful to the host. *See,* e.g., paragraphs [0071] and [0084] of the application as published. In particular, since the presently claimed compositions elicit a mucosal humoral immune response against an endogenous prion protein when administered mucosally, any associated Th-1-type CTL response would lead undesirably to autoimmune toxicity. Further, Th-1 mediated phagocytosis of infectious prions, which are resistant to degradation, may speed up prion infection, instead of preventing it. *See,* e.g., Wisniewski et al., Rev. sci. tech. Off. int. Epiz., 2007, 26(1): 243-251, 2007; Aucouturier et al., 2000, 96: 79-85; Wisniewski and Boutajangout, Mount Sinai Journal of Medicine, 2010, 77: 17-31; attached as Exhibits A, B and C, respectively.

Bachmann discloses compositions of which an essential component is a virus-like particle (VLP). VLPs induce a potent Th-1-type CTL response, not "a primarily Th-2 immune response ... not associated with a primarily Th-1-type CTL response" as required by Claim 1, when administered mucosally.

For example, the article by Shi et al. (J. Virol., 2001, 75(21): 10139-10148; attached as Exhibit D), which was available to the skilled artisan at the time of the present invention, discloses that VLPs induce strong Th-1-type CTL responses following mucosal immunization:

> ... PV *VLPs* actually serve as an adjuvant for the DNA plasmids to *induce CTL responses*. Because the VLPs that are used to package the plasmid DNA can induce VLP-specific T-helper responses, the T-helper cells might *enhance the generation of CTLs* specific for the antigen encoded by the plasmid through bystander action. Indeed, the *VLPs can induce a strong Th1 response* ([citations omitted]); thus, it is likely that IL-2 produced by the Th1 cells amplifies the proliferation of CTLs ... *Oral immunization with PV pseudoviruses induced mucosal and systemic CTL responses*.

(Emphasis added.) *See*, Shi et al. at page 10146, 2nd col.

Similarly, the article by Dupuy et al. (Microb Pathog., 1997, 22(4):219-25; attached as Exhibit E), which was also available to the skilled artisan at the time of the invention, discloses that VLPs elicit primarily Th-1-type CTL responses:

> Recombinant human papillomavirus (HPV) type 16 L1 *virus-like particles (VLPs)* expressed in the baculovirus system were used to investigate the cellular immune response to human papillomavirus type 16... A significant proliferative response was observed which was associated with *secretion of both interferon-gamma and interleukin-2* [(Th-1 cytokines)]. FACS analysis of splenic lymphocytes revealed that *CD8+ T-cells* [(CTLs)] were increased in the immunized mice. These results demonstrate that HPV 16 L1 *VLPs induce a T-cell response characterized by a Th1 profile*...
>
> (Emphasis added.) *See,* Dupuy et al. at Abstract.

Claim 1 requires that the composition elicits a primarily Th-2-type immune response not associated with a primarily Th-1-type CTL response, when introduced to a mammalian mucosal immune system. Bachmann does not disclose any compositions having this functional property. Bachmann discloses only VLP-containing compositions which, in fact, have an opposite functional property, since, as shown by Shi et al. and Dupuy et al. *(supra)*, they induce a primarily Th-1-type CTL immune response upon mucosal administration.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil. Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987); MPEP §2131.

In light of the above arguments and standards, applicants submit that Claim 1 is patentable over Bachmann. Applicants respectfully request that the anticipation rejection of Claim 1 be withdrawn.

III. Obviousness Rejections

Claims 3, 4, 9, 10, which all depend from Claim 1, remain rejected under 35 U.S.C. § 103(a) as being obvious over Bachmann in view of one or more of the following secondary references: Gizurarson et al. (U.S. Patent No. 6,514,503) ("Gizurarson"), Peretz et al. (Nature 2001, Vol. 412, p. 739-743) ("Peretz"), Kaneko et al. (JMB, 2000, Vol. 295, p. 997-1007) ("Kaneko"), Benkirane et al. (Journal of Biological Chemistry, 1993, Vol. 268, p. 26279-26285) ("Benkirane"), Clements et al. (US Patent No. 6,440,423) ("Clements"), and Kleanthous et al. (US Patent No. 6,585,975) ("Kleanthous").

Claim 20 and its dependent Claims 22, 23, 28, 45-53, and 55 remain rejected under 35 U.S.C. § 103(a) as being obvious over Bachmann in view of one or more of the following secondary references: Gizurarson et al. (U.S. Patent No. 6,514,503) ("Gizurarson"), US Patent 5,733,760 by Lu et al. ("Lu"), Chabalgoity et al. (Vaccine, 2001, Vol. 19, p. 460-469, in IDS of 11/18/2005) ("Chabalgoity"), Benkirane et al. (Journal of Biological Chemistry, 1993, Vol. 268, p. 26279-26285) ("Benkirane"), Kotloff (Infection and Immunity, 2002, Vol. 70, p. 2016-2021) ("Kotloff"), Peretz et al. (Nature 2001, Vol. 412, p. 739-743) ("Peretz"), and Kaneko et al. (JMB, 2000, Vol. 295, p. 997-1007) ("Kaneko").

As Claim 55 has been canceled, the rejection of this claim is rendered moot.

With respect to the remaining claims and new Claim 56 (which depends from Claim 1), the rejection is respectfully traversed.

Claims 1 and 20 have been amended to recite that the composition "when introduced to a mammal's mucosal immune system, elicits a primarily Th-2-type immune response against an endogenous prion protein of said mammal that is associated with a mucosal IgA humoral immune response and any concomitant immunoglobulin counterpart in other bodily fluids, and is not associated with a primarily Th-1-type cytotoxic T-lymphocyte response." All other rejected claims depend from claim 1 or Claim 20.

Bachmann discloses compositions of which an essential component is a virus-like particle (VLP). As explained in detail in the previous section, upon mucosal administration, VLPs induce a potent Th1-type CTL response, not a primarily Th-2-type immune response not associated with a primarily Th-1-type CTL response as required by the present claims. Thus, Bachmann does not disclose or suggest any compositions recited in the present claims.

Secondary references do not cure the deficiency of Bachmann as, even if combined, they do not disclose or suggest any compositions which are recited in the present claims, i.e., compositions which (i) contain or express a *non-infectious, non-pathogenic* mammalian prion protein selected from the group consisting of mouse, bovine, deer, elk, and sheep prion protein, (ii) are suitable for *mucosal* administration, and (iii) when introduced to a mammal's mucosal immune system, elicits a *primarily Th-2-type immune response against an endogenous prion protein* of said mammal that is associated with a mucosal IgA humoral immune response and any concomitant immunoglobulin counterpart in other bodily fluids, and is not associated with a primarily Th-1-type CTL response. Furthermore, as discussed in more detail below, none of the secondary references teach that Bachmann's VLP-containing compositions can be prevented from eliciting a potent Th1-type CTL response when administered mucosally. Thus, the skilled artisan could not have combined Bachmann with any of the cited prior art references to arrive at the presently claimed composition.

Gizurarson discloses glycerides as adjuvants for inducing mucosal immune responses to an antigen. Gizurarson does not, however, teach compositions for mucosal immunization that elicit a primarily Th-2-type immune response that is not associated with a primarily Th-1-type CTL response, as required by the present claims. In contrast, Gizurarson discloses that the immune response to the antigen includes the stimulation of CTLs. *See*, Gizurarson, col. 8, lines 16-27. Thus, combining Bachmann with Gizurarson does not result in the compositions recited in the present claims.

Clements teaches CT-B as an adjuvant. Clements does not disclose or suggest any compositions containing or expressing a *non-infectious, non-pathogenic* antigen that, when

introduced to a mammal's mucosal immune system, elicits a primarily Th-2-type immune response against an *endogenous* antigen of said mammal, as required by the present claims. In contrast to the present claims, Clements discloses eliciting immune responses against either *pathogenic* antigens (e.g., pathogenic strains of bacteria, col. 12, line 40 – col. 13, line 9) or against *non-endogenous* proteins (e.g,. ovalbumin (OVA) (see col. 7, lines 9-39).

Kleanthous discloses the covalent attachment of CT-B to antigenic proteins. Kleanthous does not disclose or suggest any compositions containing or expressing a *non-infectious, non-pathogenic* antigen that, when introduced to a mammal's mucosal immune system, elicits a primarily Th-2-type immune response that is not associated with a primarily Th-1-type CTL response, as required by the present claims. In contrast to the present claims, Kleanthous only teaches eliciting a Th-1 response through parenteral administration.

Lu and Chabalgoity teach effectiveness of Salmonella vectors in induction of mucosal immune responses. The present claims require the Shigella or Salmonella strain to be transformed with a vector capable of expressing a *non-infectious, non-pathogenic* mammalian prion protein, and not an antigen derived from an infectious pathogenic agent such as a bacteria or virus. In contrast to the present claims, Lu and Chabalgoity only disclose compositions expressing antigen derived from *infectious pathogenic* agents. See, e.g., Lu at col. 4, lines 47-49 (HIV antigen); Chabalgoity at page 466, 2nd col., ("live recombinant Salmonella that express heterologous antigens from other pathogens").

Furthermore, in contrast to the present claims, neither Lu nor Chabalgoity teaches or suggests any compositions that, when introduced to a mammal's mucosal immune system, elicits a primarily Th-2-type immune response that is not associated with a primarily Th-1-type CTL response. In fact, Lu discloses that the Salmonella vectors induce Th-1 responses (see Lu at col. 4, lines 53-64). Similarly, Chabalgoity discloses that the Salmonella typhimurium vectors expressing pathogenic antigens induced Th-1 responses, even when administered mucosally (see, Chabalgoity at page 466, 2nd col., last paragraph; emphasis added):

> ELISA analysis of the IgG subclasses of the antigen-specific antibody response, shows a clear polarization towards the IgG2 subclass for all antigens tested. Using the *salmonella* delivery system for studies conducted in mice, it has been shown that the immune responses elicited are *biased to a Th1 profile*.

Kotloff discloses eliciting anti-Shigella immune responses. However, Kotloff does not disclose or suggest any compositions suitable for mucosal administration and comprising a bacterial vector expressing a non-infectious, non-pathogenic mammalian prion protein, as required by the present claims.

Peretz and Kaneko teach specific regions of prion protein but do not disclose any compositions suitable for mucosal administration or capable of eliciting a primarily Th-2-type immune response against an endogenous prion protein of said mammal that is associated with a mucosal IgA humoral immune response and any concomitant immunoglobulin counterpart in other bodily fluids, and is not associated with a primarily Th-1-type CTL response, when introduced to a mammal's mucosal immune system.

Benkirane discloses that D-residues increase the antigenicity of antigenic peptides and lead to the generation of high levels of IgG3 antibodies. This reference does not disclose or suggest any of the composition properties (i)-(iii) recited in the present claims.

Taken together, even if combined, the cited references do not disclose or suggest the compositions recited in the present claims.

In light of the foregoing arguments, the present claims are not obvious over the cited prior art. Withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

In view of the above arguments and amendments, it is respectfully submitted that the present claims are now in condition for allowance and such action is earnestly solicited. If the Examiner believes that a telephone conversation would help advance the prosecution in this case, the Examiner is respectfully requested to call the undersigned attorney at (212) 641-2364. The Commissioner is hereby authorized to charge all requisite fees to our Deposit Account No. 06-1050.

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Respectfully submitted,

By /Irina E. Vainberg/
Irina E. Vainberg
Registration No.: 48,008
Fish & Richardson P.C.
601 Lexington Ave.
52nd Floor
New York, NY 10022
212-641-2364
877-769-7945 (fax)
Attorneys/Agents For Applicant